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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HABTE, KAHSAY	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 11/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/702,302	MAAG ET AL.	
	Examiner	Art Unit	
	Kahsay Habte, Ph. D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-16,33-44 and 47-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-3,5-16,33-43 and 47-50* is/are allowed.

6)☒ Claim(s) *44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3, 5-16 and 33-50 are pending in this application:

Response to Amendment

2. Applicant's amendment filed 10/03/2005 in response to the previous Office Action (07/14/2005) is acknowledged. The enablement rejection (item 3) has been maintained. Applicants have overcome the enablement rejection (item 4) by canceling claim 46.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 44 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claim 44, it is recited a method of treating a memory disorders or Alzheimer's disease, but the specification is not enabled for such a scope.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation

necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims: Claim 44 is directed to a method of treating memory disorders or Alzheimer's disease.

a. Scope of use - The scope of use that applicants intend to claim may well be very broad. Memory disorders are conditions in which memory are disturbed. Memory disorders are extremely broad in nature. It includes cognitive disorders. Memory disorders can be organic or functional. Organic causes include damage to the brain, through trauma or disease, or use of certain (generally sedative) drugs. Functional causes are psychological factors, such as defense mechanisms. Hysterical post-traumatic amnesia is an example of this. The main cause of memory loss or disorder is a form of dementia (a loss in the brain functions responsible for thinking) caused by Alzheimer's disease. This progressive, degenerative disease of the brain results from the death of brain cells, causing a loss of thinking and remembering abilities. Other conditions, such as very small strokes in the brain, can cause memory loss. Note that there are over one hundred types of disorders, which can cause dementia.

Cognitive Disorders – are disorders in a brain that prevents someone from thinking

well, from solving problems, or from storing information. Three main types of cognitive disorders are: Delirium, Dementia, and Amnesia.

Delirium - is a severe disturbance in consciousness and thought that is not better accounted for by dementia. Delirium is likely to have a sudden onset, be variable, and have a better chance of remission than dementia. Delirium involves disorientation and memory loss, along with distorted consciousness and cognitive deficits. The victim may not know what time it is, or where she or he is, or be able to speak coherently. Short-term memory loss is almost always noted. The patient is usually agitated, with the agitation worse at night; if in the hospital, the patient may fight, break things or tear out intravenous tubes, and have to be restrained. The onset of delirium is typically fairly sudden, taking a few hours to a few days, and delirium rarely lasts for more than a month; unfortunately, one reason for this is that the patient may die. Especially for this reason, the occurrence of delirium is a clear medical emergency calling for prompt treatment. One cause of delirium is substance intoxication via overdoses of drugs or exposure to toxins, or withdrawal from drugs. Another is various medical conditions, brain trauma caused by an accident or stroke, for example. The type of delirium is determined by what caused it; for example, two types are substance intoxication delirium and delirium caused by a medical condition.

If intoxication or treatable medical problems are detected and treated, the delirium is probably reversible. If treatment is not possible, permanent brain damage is either present or likely to develop, and the delirium may progress to dementia.

Delirium can be subcategorized into one of the following depending on the causes:

From substance intoxication

From withdrawal

From multiple causes

Other cognitive disorders include autism, ADHD, schizophrenia, and other forms of psychosis.

Dementia, like delirium, involves cognitive deficits, but the deficits are different. One universal characteristic of dementia is short-term memory loss. It may be accompanied by inability to find words (aphasia), to recognize objects (agnosia), or to carry out a sequence of motor activities (apraxia), despite the ability to make the individual movements. The onset of dementia tends to be more gradual than the onset of delirium, and may go unnoticed for long periods. The person with dementia may behave quite inappropriately, for example by telling dirty jokes to strangers or exposing genitalia. Violent behavior, although less common than in cases of delirium, sometimes occurs. In early cases of dementia, when the individual is aware of his or her deteriorating condition but still able to execute plans, suicide is a possibility.

Just as in delirium and many other disorders, the subtypes of dementia are classified according to their causes. An increasingly common type of dementia is dementia of the Alzheimer's type; estimates place the percentage of people over 65 in the United States with Alzheimer's at 2 to 4 percent.

Despite the fact that many causes of dementia are age-related, one should not assume that dementia is a normal consequence of aging. Although little can be done to prevent or ameliorate dementia in many cases, a medical examination is necessary in order to evaluate causes and possible treatments. One study of cases of dementia at three centers showed that 26% of the cases were treatable. The most common treatable cases are those with chronic drug toxicity, major depression, normal pressure hydrocephalus, or operable brain masses.

Future research may uncover, one type at a time, ways to prevent or treat the dementias; some drugs already show promise in arresting the progress of Alzheimer's disease. Other types of dementia include: Alzheimer's Disease, Creutzfeldt-Jacob Disease, HIV Dimentia, Pick's Disease, Vascular Dementia, Substance-Induced Persisting Dementia, Dementias that can arise from head trauma, Huntigton's Disease, Parkinson's disease.

Amnesia - is loss of memory; it is retrograde if memories before a fixed event are lost, and anterograde if memories after a fixed event are lost. An individual may have both kinds of amnesia.

Amnesias, as the name indicates, are characterized by memory losses without sufficient cognitive deficits to indicate a diagnosis of delirium or dementia, and can be subcategorized into those: Caused by medical conditions, Caused by substance abuse, etc.

As shown above, memory disorders are very broad in nature and the disorders also vary one from the other.

In claim 44, a method of treating Alzheimer's disease is recited. The central characteristic of Alzheimer's disease is the deficiency in the level of the neurotransmitter Acetylcholine that plays an important role in memory or it is believed that too much stimulation of nerve cells by glutamate may be responsible for the degeneration of nerves that occur in Alzheimer's disease. Like other neurotransmitters, glutamate is produced and released by nerve cells in the brain. The released glutamate then travels to nearby nerve cells where it attaches to a receptor on the surface of the cells called the N-methyl-D-aspartate (NMDA) receptor. Drugs such as memantine blocks the receptor and thereby decreases the effects of glutamate. It is thought that by blocking the NMDA receptor and the effects of glutamate, memantine may protect nerve cells from excess stimulation by glutamate.

b. Scope of Compounds - The scope of the compounds is also broad. It is apparent that hundreds of millions of combinations of compounds can be created from the definitions, owing especially to broad scope of R^1-R^9, X, Z, p and q.

(2). Direction of Guidance: Applicants indicate that 5-HT2 selective and 5-HT6 selective ligands have been identified as potentially useful in the treatment of certain CNS disorders such as Parkinson's disease, Huntington's disease, anxiety, depression, manic depression, psychoses, epilepsy, obsessive compulsive disorders, mood disorders, migraine etc. The amount of direction or guidance is minimal. There is no

guidance for the treatment of memory disorders or Alzheimer's disease that are related or affected by 5-HT2 or 5-HT6 receptors. Dosage (1-500 mg (500 fold) is generic to the disorders - same dosage for all disorders.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to these benzomorpholine derivatives recited in claim 1 as 5-HT ligands or indeed are in use for the treatment of memory disorders or Alzheimer's disease recited in claim 44.

(4). Working Examples: At page 55 of the specification, an example of *in vitro* radioligand binding studies of Compound of Formula I was determined, but there is no way to convert this data into specific useful knowledge, especially in view of the difficult nature of some of these disorders. There is no link between the Ki values and memory disorders or Alzheimer's disease. Applicants' compounds were tested and found to be selective 5-HT6 antagonists according to page 56.

(5). Nature of the Invention and Predictability: The invention is directed to treating memory disorders that are related or affected by 5-HT receptors. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Memory disorders are especially unpredictable due to their complex nature.

The treatment of one type of memory disorder could not be necessarily the same for the other type.

(6). The Relative Skill of Those in the Art: The relative skill is extremely very low. To this day, there is no magic bullet that can treat memory disorders in general. Many memory disorders have no treatment at all, e.g. dementia or amnesia.

Note that applicants' compounds are indicated as 5-HT receptors, but the claims are not limited to this. The radioligand binding test indicates that the compounds are 5-HT6 antagonists. According to a review article by Russell MG and Dias R. (Curr. Top. Med. Chem, 2002 June; 2(6):643-54), "the study for the possible role of 5-HT(6) receptor antagonists in the treatment of learning and memory disorders has stimulated significant recent work in this area", indicating that the study is at its early stage. According to the article (page 652, first paragraph), it has been concluded: "these data are open to very different interpretations which directly oppose the proposed role for 5-HT6 receptor antagonists as potential enhancers." The above statement surely contradicts the use of applicants' compounds for the treatment of memory disorders or Alzheimer's disease as recited in claim 44. This fundamental, unresolved contradiction shows how low is skill level in this art.

According to said article (page 650, last paragraph), it has been cited that "the current lack of full data supporting a role for 5-HT6 receptor antagonists in either behavioral inflexibility or in cognition enhancement *per se*, ...Certainly, the findings from

both water maze studies are interesting and follow-up studies would be recommended." The article clearly shows that supporting data is needed for the role of 5-HT6 receptors as antagonists in behavioral inflexibility or in cognition enhancement, and that basic understanding is still lacking.

According to the article (see 648, second column last paragraph): "there are a number of potential problems regarding the behavioral findings described above. One concern is the relatively poor brain penetration ...". The cited reference in the conclusion (page 652) points out that additional studies are required to both replicate and further investigate the functional role of the 5-HT6 receptor. In fact the authors concluded: "Indeed, to date, findings from *in vivo* studies which have attempted to shed light on 5-HT6 receptor function are ambiguous and somewhat controversial." It is clear from the article that the study is at its early stage as of June 2002 (after the filing date of the instant case). It certainly require undue experimentation to determine which central nervous system disorders are related or affected by the 5-HT6 receptors given how little is actually known about the function of 5-HT6 receptor. Despite the discrepancies noted on the article in regard to the research, applicants intend to claim the treatment of memory disorders or Alzheimer's disease. It is up to applicants to provide a publication that shows that their compounds can act as agonists or antagonists to treat memory disorders that are related or affected by 5-HT receptors especially by 5-HT6 receptor as indicated in the working example.

In regard to Alzheimer's disease, Alzheimer's disease can be treated by Acetylcholinesterase inhibitors that reduce the depletion of acetylcholine or by drugs

that inhibit NMDA receptor. The skill level in the art is so low that the only treatments available to this day are drugs that inhibit Acetylcholinesterase or drugs that inhibit NMDA receptor that decreases the effects of glutamate. Applicants' compounds do not do this. Thus, the enablement rejection is proper.

(7). The Quantity of Experimentation Necessary: Immense, because of points (1), (2) and (6).

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Response to arguments

Applicant's argument filed 10/03/2005 has been fully considered but it is not persuasive.

Applicants have cancelled claim 45 and 46 and amended claim 44 to overcome the enablement rejection raised in previous Office Action (see item 3). Applicants have amended claim 44 by limiting CNS diseases to "memory disorders or Alzheimer's

disease", but this amendment would not overcome the first paragraph rejection, see above.

Applicants argue: "5-HT6 antagonist has been specifically shown by Woolley et al., "A Role for 5-HT6 Receptors in Retention of Spatial Learning in the Morris Water Maze", Neuropharmacology 41, 210-219 (**2001**). The memory enhancing effects of 5-HT6 antagonists in the water maze test were also confirmed by Rogers et al., "5-HT6 Receptor Antagonists Enhance Retention of a Water Maze Task in the Rat", Psychopharmacology 158, 114-119 (**2001**). Improved learning consolidation in rats subject to autoshaping tasks following treatment with a 5-HT6 receptor antagonist has been shown by Meneses, "Role of 5-HT6 Receptors in Memory Formation", Drug News Perspect. 1447), 396-400 (**2001**). Additional exemplary publications linking 5-HT6 antagonists to treatment of memory disorders are: Riemer et al., "Influence of the 5-HT6 Receptor on Acetylcholine Release in the Cortex ", J. Med. Chem. 46, 1273-1276 (**2003**); Dawson et al., "In Vivo Effects of the 5-HT6 antagonist 58-271046 on Striatal and Frontal Cortex Extracellular Concentrations of Noradrenaline, Dopamine, 5-HT, Glutamate and Aspartate", British J. Pharmacology 130, 23-26 (**2000**); Branchek et al., "5-HT6 Receptors as Emerging Targets for Drug Discovery", Ann. Rev. Pharmacol. Toxicol. 40, 319-334 (see p. 329 in particular) (**2000**); Woolley et al., "Reversal of a Cholinergic-Induced Deficit in a Rodent Model of Recognition Memory by the Selective 5-HT6 receptor Antagonist Ro 046790", Psychopharmacology 170, 358-367 (**2003**); Dawson et al., "5-HT6 Receptor Antagonist 58-271046 Selectively Enhances Excitatory

Neurotransmission in the Rat Frontal Cortex and Hippocampus", Neuropsychopharmacology 25 No. 5, 662-668 (**2001**); and Tsai et al., "Association Analysis of the 5-HT6 receptor polymorphism C267T in Alzheimer's Disease", Neuroscience Lett. 276, 138-139 (**1999**). Copies of these publications (which predate Applicants' filing date) are submitted herewith."

Applicants argue that "link between treatment of memory disorders and the 5-HT6 receptor is well established in the Scientific literature". In regard to the references submitted by applicants, none of the articles link the treatment of memory disorders or Alzheimer's disease to that of 5-HT6 receptor antagonists. For example, Woolley et al. discloses in the abstract "5-HT6 antagonist administration strongly indicate a role for this receptor in memory process". This shows that the 5-HT-6 receptor is somehow related to the memory process, but not to the treatment of memory disorders or Alzheimer's disease. Roger et al. disclose in the abstract "5-HT6 receptors are predominantly located in the brain and may be involved in cognitive processes." This article by Roger et al. also shows no disclosure that link the treatment of memory disorders or Alzheimer's disease what is claimed in claim 44. In regard to the other references, none of the references link the treatment of 5-HT6 receptor to the treatment of memory disorders or Alzheimer's disease.

Claim 44 is drawn to a method of treating memory disorders or Alzheimer's disease that are not limited to 5-HT6 receptor antagonists. Even if the compounds are limited to 5-HT6 receptor antagonists for the treatment of memory disorders or

Alzheimer's disease, applicant's response is not persuasive enough to overcome the rejection.

Conclusion

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson (Acting SPE) can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kahsay Habte, Ph. D.
Patent Examiner
Art Unit 1624

11/1/2005